Late abdominal aortic aneurysm enlargement after endovascular repair with the Excluder device

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Objectives: **Behavior of the abdominal aortic aneurysm (AAA) sac after endovascular abdominal aortic aneurysm repair (EVAR) is graft-dependent. The Excluder endograft has been associated with less sac regression than some other stent grafts. Long-term follow-up has not been reported.**
Methods: **Between May 1999 and July 2002, 50 patients underwent EVAR with the Excluder bifurcated endoprosthesis. These patients were followed up prospectively with computed tomography (CT) at 1, 6, and 12 months and yearly thereafter. One immediate conversion to open surgery and three deaths occurred within 6 months. One additional patient was lost to follow-up. The remaining 45 patients, 35 men and 10 women, were followed up for at least 1 year, and form the basis for this report. Their mean age was 73 ± 5.5 years. The minor axis diameter at the largest area of the AAA on CT examination was compared with the baseline measurement at 1 month and to the smallest size previously recorded during follow-up. Change in sac size of 5 mm or greater was considered significant. Mean follow-up was 2.7 ± 1.2 years (range, 1-4 years). Nominal variables were compared with the χ^2 test, and continuous variables with the Student *t* test.**
Results: **A significant decrease in average AAA sac diameter was observed at 6-month, 1-year, and 2-year follow-up. These differences were lost by the 3-year evaluation, because of delayed sac growth (n = 9) and re-expansion of once shrunken aneurysms (n = 3). The probability of freedom from sac growth or re-expansion at 4 years was only 43%. At last follow-up, sac expansion occurred in the absence of active endoleak in nine patients. Type II endoleak was associated with sac expansion in three patients ($P = .003$), resulting in one conversion to open surgery after the 4-year follow-up. No graft migrations, AAA ruptures, or aneurysm-related deaths were noted.**
Conclusions: **Late aneurysm sac growth or re-expansion after EVAR with the Excluder device is common, even in the absence of endoleak. Although the incidence of important clinical sequelae is low at this point, the incidence of aneurysm expansion should be taken into consideration during the risk-benefit assessment before EVAR repair with the Excluder device. (J Vasc Surg 2004;39:1236-42.)**

Since it was first reported in 1991,[1] endovascular repair (EVAR) of abdominal aortic aneurysms (AAA) has resulted in the introduction of many commercial devices intended for the treatment of aneurysmal disease. To date four endograft devices (Ancure, Guidant; AneuRx, Medtronic/AVE; Excluder, W. L. Gore & Associates; Zenith, Cook) have been approved by the Food and Drug Administration (FDA). Three remain commercially available.

As midterm and long-term results are emerging, device-specific clinical outcomes with respect to frequency of endoleak, incidence of device migration, risk for limb thrombosis, and change in aneurysm sac size have been recognized. Each device has been associated with disparate long-term results. Previous reports have suggested that the type of endograft is strongly correlated with the likelihood of sac regression.[2] While shrinkage of the aneurysm sac after EVAR may be desirable, a stable aneurysm has never been linked to any untoward effects. Sac enlargement, however, implies elevated pressure in the aneurysm sac, and so far has been associated mainly with endoleak. Few isolated cases of sac enlargement after Excluder implantation have been documented and linked to the presence of a sac hygroma.[3,4] The exact extent of this phenomenon is not known. We reviewed our experience with the first 50 patients to determine the frequency of late sac enlargement after EVAR with the Excluder device.

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PATIENTS AND METHODS

Between May 1999 and July 2002, 50 patients underwent EVAR with the Excluder bifurcated endoprosthesis at the University of Pittsburgh Medical Center. All patients were part of the multiple-phase trials of the device before FDA approval, and signed a research informed consent form. All data were and continue to be collected prospectively, according to the trial protocols. The institutional review board at the University of Pittsburgh School of Medicine approved all the multiphase trial protocols.

All patients underwent preoperative spiral computed tomography (CT) with 2.5 mm collimation. Preoperative angiography was used only when length measurements could not be accurately determined from CT images and in cases of unusual anatomy. Postoperative CT scans were obtained with and without contrast material enhancement at 1, 6, and 12 months, and yearly thereafter. Four-view plain radiographs were also obtained at each follow-up visit, and were evaluated for modular disconnection or device migration.

The method used for measuring changes in dimension of the aneurysm was in accordance with the Society for Vascular Surgery reporting standards for endovascular aortic aneurysm repair.[5] To avoid interobserver variability all measurements were prospectively performed by the senior author (M.S.M.), using digital electronic calipers on a computer workstation with commercially available software (Stentor). Aneurysm sac size was defined as the minor axis on the largest axial cut of the aneurysm on the two-dimensional CT scan. The minor axis was chosen to avoid overestimation of AAA size due to tortuosity of the aorta.[6] The 1-month postoperative CT scan served as the reference scan against which all subsequent measurements were compared to determine aneurysm sac expansion or shrinkage. Changes of 5 mm or more in the minor axis were considered significant for either enlargement or shrinkage.[7] Because some patients exhibited an initial reduction in size followed by later enlargement, this phenomenon was referred to as re-expansion. The re-expansion was also considered significant at 5 mm above the smallest measured diameter during follow-up.

The presence or absence of endoleak was determined from CT scans with and without contrast enhancement. Patients with persistent endoleak after 6 months of observation or with delayed-onset endoleak underwent angiography and, when feasible, coiling of the responsible branch vessels. Those with sac expansion and no demonstrable endoleak were followed up with CT scans at closer intervals. Angiography was performed in two such patients at 3.5 and 4 years, respectively, to look for occult endoleak; none was detected. Graft migration was defined as longitudinal movement in the attachment sites of at least 10 mm.

Nominal variables were compared with the χ^2 test, and continuous variables with the Student t test. Results are reported as mean ± SD.

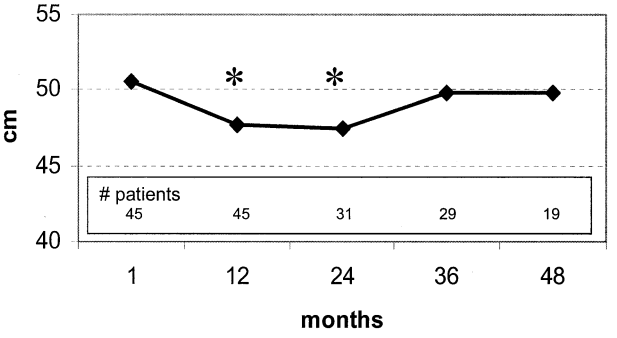

Fig 1. Average abdominal aortic aneurysm sac size at each follow-up interval. *$P < .05$ compared with 1 month value.

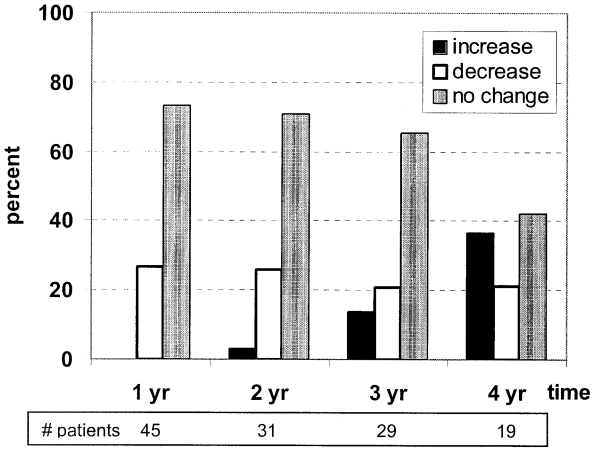

Fig 2. Percentage of patients with enlarged, reduced, or stable abdominal aortic aneurysm sac size at each follow-up interval compared with baseline measurement.

RESULTS

Clinical results. There were no perioperative deaths. One patient underwent immediate open conversion when a left renal artery was inadvertently covered by an aortic extender placed in an angulated neck to achieve a proximal seal. No limb occlusion, aneurysm rupture, graft migration, or limb dislocation was noted during follow-up. One patient underwent placement of an aortic cuff extender at 1 year, to reinforce the severely angulated proximal attachment site. Three patients died before reaching 6-month follow-up, from renal-related and cardiac-related causes. One additional patient was lost to follow-up. The remaining 45 patients (35 men, 10 women; mean age, 73 ± 5.5 years) completed at least 12 months of follow-up, and form the basis for the size change analysis. Late deaths occurred in seven patients during follow-up, from unrelated causes. Four additional patients withdrew from the study because of health-related and geography-related issues. The last CT images were obtained at a mean of 2.8 ± 1.2 years. Twenty-eight patients (62%) were followed up for 3 or more years, and 19 patients (42%) for 4 years.

Size change. Mean AAA sac size at 1-year (47.7 mm) and 2-year (47.4 mm) follow-up was significantly reduced compared with the reference scan (50.5 mm). These differences were lost by the 3-year (49.8 mm) follow-up, which suggests delayed sac growth and re-expansion (Fig 1). The proportion of patients with change in aneurysm size in comparison with the reference scan at each time point is shown in Fig 2. With longer follow-up a larger proportion of patients exhibited an expanding aneurysm sac compared with the reference scan. By 4 years, 37% of patients exhibited significant enlargement of the aneurysm sac, whereas only 21% showed significant size reduction.

At last follow-up, sac enlargement or re-expansion was observed in 12 patients and sac shrinkage in 10 patients. All but one of the enlargements was delayed in onset for at least 3 years after implantation. One sac enlargement was detected at the 2-year follow-up examination (Fig 3). This is in contrast to sac regression, which was usually observed early, and noted within 12 months in 13 patients (Fig 4). One patient was even noted to have a significant sac reduction at 1 month compared with the preoperative CT scan,

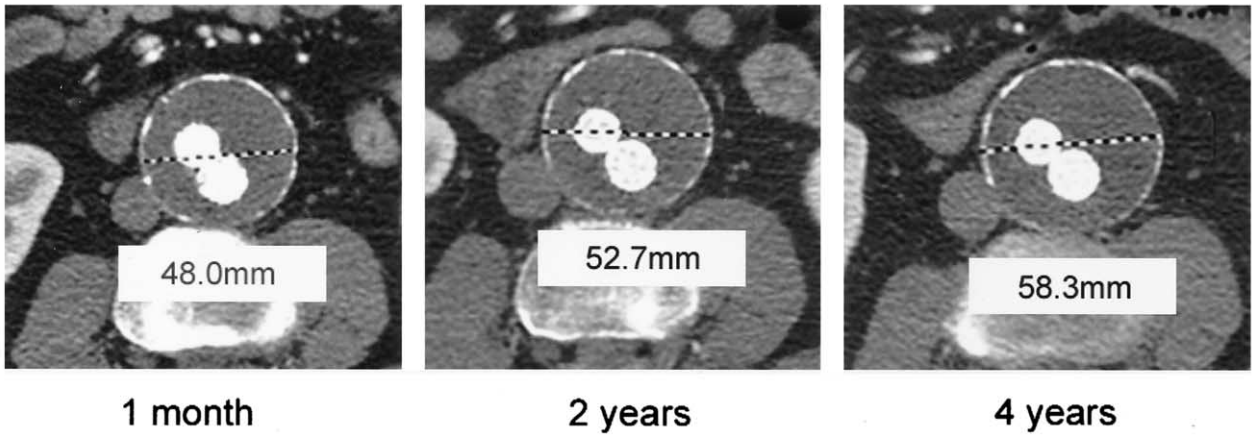

Fig 3. Serial computed tomography scans demonstrate gradual increase in abdominal aortic aneurysm sac size after implantation of the Excluder device.

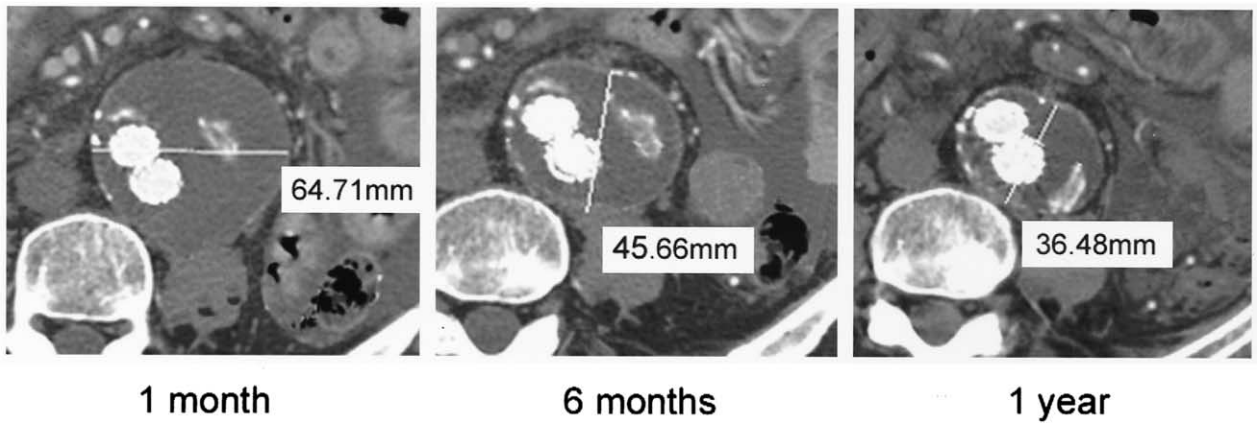

Fig 4. Serial computed tomography scans demonstrate rapid decrease in abdominal aortic aneurysm sac size after implantation of the Excluder device.

and the sac continued to shrink during the entire follow-up period.

It is noteworthy that three sac enlargements were re-expansions after initial shrinkage of more than 5 mm. In one patient the sac had regressed by 10 mm by the 6-month follow-up, with slow re-expansion to baseline by the fourth year (Fig 5). In the second patient the sac regressed from 55 mm to 48 mm by the 6-month follow-up, and slowly re-expanded to 54 mm at 4 years. In the third patient the sac had shrunk from 49 mm to 42 mm at 6 months, only to re-expand to 47 mm at 3 years, and to 49 mm at 4 years.

A Kaplan-Meier estimate of probability of freedom from sac enlargement as compared with the reference scan was 97% at 2 years, 86% at 3 years, and 57% at 4 years (Fig 6). This method of comparison, however, does not take into consideration those sacs that re-expanded after initial regression, because the last aneurysm size did not differ significantly from the reference value. A Kaplan-Meier estimate of probability of freedom from sac enlargement as compared with the reference scan or the smallest size at any follow-up time point was 95%, 80%, and 43%, respectively, for the same periods of observation (Fig 7). Both plots indicate frequent expansion rates after the third year of observation.

Endoleak effects. There were no type I or type III endoleaks. A type II endoleak was detected in eight patients (18%), with spontaneous resolution in five patients. One patient with spontaneous resolution of a type II endoleak at 12 months exhibited delayed sac growth at the 4-year follow-up visit. After 3 years of stable size, the sac enlarged from 52 mm to 62 mm in 1 year without any evidence of endoleak at either CT scanning or angiography. All three patients with persistent endoleak underwent angiography for attempted treatment. In one patient the endoleak could not be identified; in the other two patients coil embolization of lumbar endoleaks was successful. In both of these patients, however, the leak failed to be completely obliterated at long-term follow-up. All three patients exhibited sac

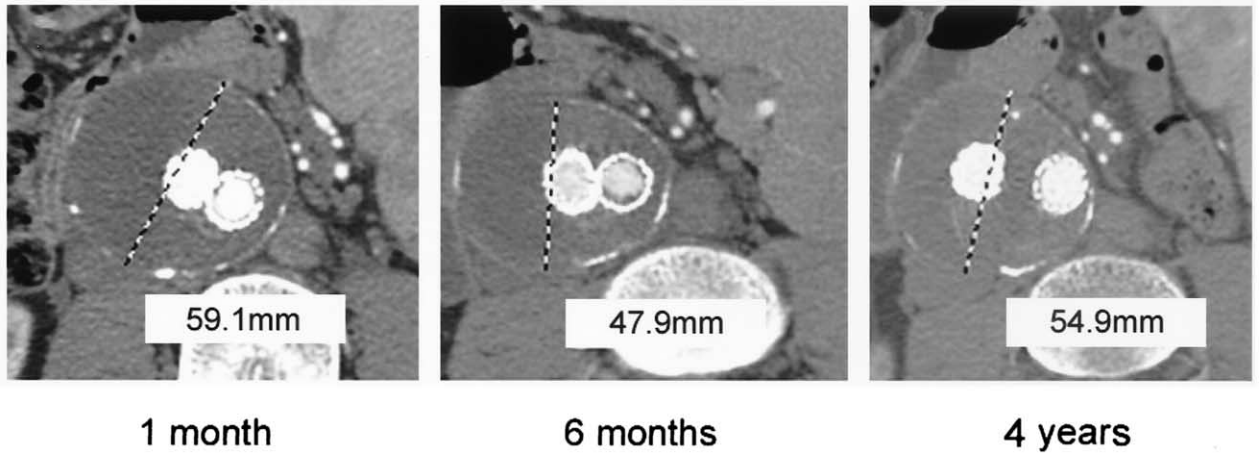

Fig 5. Serial computed tomography scans demonstrate initial decrease in abdominal aortic aneurysm sac size, followed by re-expansion.

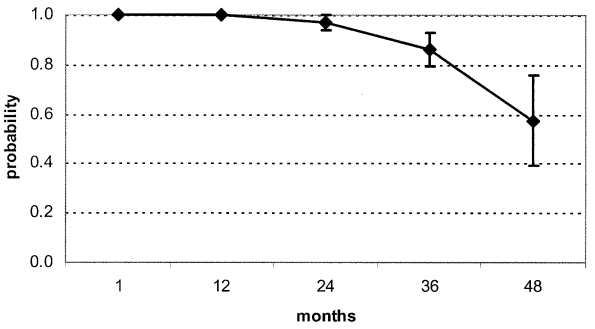

Fig 6. Probability of freedom from aneurysm sac enlargement compared with baseline after repair of abdominal aortic aneurysm with the Excluder device.

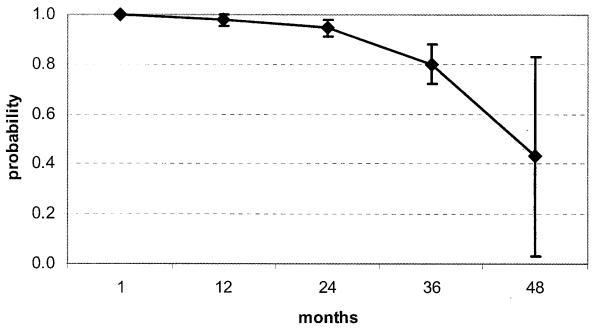

Fig 7. Probability of freedom from aneurysm sac growth or re-expansion after repair of abdominal aortic aneurysm with the Excluder device.

enlargement at 4 years, ranging from 7 to 13 mm. One of these patients underwent conversion to open repair; the other two patients are still being observed.

In nine of 12 patients sac expansion developed, ranging from 6 to 11 mm, in the absence of any active endoleak. History of endoleak was not associated with sac enlargement ($P = .08$, χ^2). This may represent a type II error due to the small number of patients. Early sac shrinkage by either 6 months or 1 year did not provide any protective effects against delayed aneurysm expansion. Smaller aneurysms (<5 cm) exhibited a higher incidence of sac shrinkage than did larger aneurysms ($P = .046$).

DISCUSSION

Several recent reports have shown that change in aneurysm size after EVAR is endograft-dependent.[2,8,9] The Excluder and AneuRx devices had a sharply lower incidence of shrinkage compared with the other endografts. The clinical significance of these changes, however, is not entirely clear. Although shrinkage of the sac may be reassuring, it does not necessarily indicate complete exclusion, inasmuch as some patients may show regression in the presence of small endoleaks.[9,10] Reduction in sac size is not universal, and many patients show no significant change over a long period despite adequate exclusion by most methods of assessment. A stable sac is clinically benign, and has even been considered desirable in the early endograft experience, because it averts inducing stresses on modular junctions with the changing geometry of a shrinking AAA.[11] Concern during follow-up is usually elicited only by an enlarging sac, because it has most often been associated with significant endoleak and anticipation of possible rupture. Though infrequent, an enlarging sac without demonstrable endoleak has been reported on several occasions,[3,12,13] and has been attributed to "endotension," a state of increased pressure in the excluded sac. The incidence of such enlargement has been unusual, representing a small fraction of patients treated with EVAR.[2,10,14,15]

This is the first report indicating that a significant number of patients treated with a single endograft exhibit this unusual expansion over time, even in the absence of endoleak. Nearly 40% of the patients treated with an Excluder device had significant sac enlargement compared with baseline diameter measurement by the fourth fol-

low-up year. So far, this enlargement has not been associated with any untoward clinical events. Our only conversion so far was in a patient with a known endoleak from a set of lumbar arteries in the neck of the sac that could not be treated noninvasively.

The pathogenesis of sac enlargement with the Excluder endograft is not well known. Several open conversions in the United States and Europe have indicated the presence of highly viscous fluid or gel in the sac, without evidence of unrecognized endoleak. This has been termed by Risberg et al[3] as a sac "hygroma." Whether this represents an exudate of fluid through the graft material or from another source remains to be determined. Microleaks at suture points between stent and fabric noted with other endografts[16] have never been demonstrated with the Excluder device, which relies on a bonded film to fix the components, rather than manually placed sutures. This seems to be an unlikely source for the observed enlargement. Many other theories have been advanced, including an active fibrinolytic state that attracts fluid accumulation into the sac.[17-20] However, the absence of similar behavior with other endografts where clot absorption is also probably associated with a fibrinolytic state seems to favor transgression of fluid through the fabric, analogous to the subcutaneous implantation of expanded polytetrafluoroethylene in the periphery.[21,22] Upcoming modifications to the graft material to reduce permeability are expected soon, and should help delineate whether this is the cause of sac enlargement. Since this is the most likely theory for this behavior, this change may resolve the issue satisfactorily.

When sac enlargement coexists with endoleak, treatment has been directed at treating the endoleak, and if unsuccessful, conversion to open repair has been advocated to avert late rupture. No clear mandate exists, however, for conversion in patients with expansion of the sac in the absence of endoleak. Rupture of the sac in these patients may not be of major clinical significance. Since endoleak cannot always be reliably ruled out, the tendency is to err on the safe side, and convert to an open procedure. In addition, possible concern about short necks becoming effaced with enlarging sacs, although unproved, adds a theoretical disadvantage to long-term observation. These concerns may result in a number of late conversions if an endograft is associated with a large number of expanding sacs, as appears to be the case with the Excluder device. Alternative strategies, such as emptying the sac by means of aspiration, exploration and reclosing of the sac, or performing a window in the sac laparoscopically, are being explored by several investigators (M. R. van Sambeek, personal communication, 2003).[3] The long-term benefits of such strategies remain unconfirmed. We have continued to observe most of our patients, because of slow growth and limited size of the enlarged sac. Some are patients at high risk in whom long-term observation may be justifiable.

Despite the large number of patients exhibiting enlargement or re-expansion, the clinical results remain good at 4 years, with no migration, rupture, disconnection of limbs, or occlusion. The excellent early results[23] and the good late clinical outcomes continue to justify the use of this device, especially in patients at high risk with shortened life expectancy. In addition, physical characteristics of the device, such as low profile and flexibility, make it more suitable for use in certain anatomic situations than other available devices. Initial shrinkage, however, should not provide a false sense of security; we noted later sac expansion in several patients who had initial reduction in sac size. This should underscore the importance of vigilant follow-up for the life of the patient. The expansion process is slow, and does not manifest itself clearly until the 4-year follow-up. This may be due to a slow transudation of fluid or the use of a crude and insensitive method of measuring enlargement, such as enlargement of the diameter of the sac by 5 mm before being considered significant. Volume measurements may be more sensitive, and may enable identification of enlargement at an earlier stage.[24]

The current report is limited by the relatively small number of patients with 4-year follow-up. Awaiting the national trial data report will be important to place the incidence of this observation into proper perspective. Nevertheless, the present study raises some concern that the incidence of late sac enlargement with the Excluder device may be higher than anticipated, exceeding what has been reported with other devices. Whether this observation will translate into any kind of clinical sequelae, however, remains unclear. Until long-term behavior of this phenomenon is better understood, we recommend close follow-up of patients with sac expansion at shorter intervals, with CT and other adjunctive imaging methods, to identify and treat endoleak, if present. Conversion to open repair should be considered in the presence of an endoleak that is recalcitrant to catheter-based techniques, at the request of patients or rapid expansion of the sac. Our patients have not manifested any clinical consequences at 4 years after implantation, with the only conversion being to treat an unresolved endoleak. Investigations into the pathogenesis of this phenomenon, and strategies to deal with its sequelae remain an important challenge.

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INVITED COMMENTARY

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By careful analysis of progressive computed tomography scans during follow-up, Cho et al identified a staggering probability of freedom from sac growth or re-expansion at 4 years of only 43% after endovascular abdominal aortic aneurysm (AAA) repair with the Excluder device (W. L. Gore & Associates). Inasmuch as all measurements were prospectively performed by a single, experienced endovascular surgeon, the intraobserver error, if tested, may well have been less than the 5 mm arbitrarily chosen as significant. It is possible therefore that the figure for freedom from sac growth or re-expansion at 4 years may be even lower than 43%.

Of greater interest and concern is their finding that sac expansion occurred in the absence of active endoleak in nine of 12 patients; the remaining three patients had type II endoleaks. Although the cause of the aneurysm enlargement is not known, it must be assumed, for patient safety, to be due to raised intrasac pressure or endotension. There have been anecdotal reports of endotension previously, but this is the first report of endotension occurring in almost half of patients who received a single type of endograft.

While the method of the study is exemplary, one might question the interpretation of the findings. The authors have made an important observation, but appear to be intent on putting a favorable spin on it. They state that the excellent early results, as well as good late clinical outcomes, continue to justify the use of this device. Considering that a patient with an expanding AAA sac after endovascular repair is probably at the same risk for rupture as if nothing had been done to treat the aneurysm in the first place, it is difficult to recommend a device with a known probability of failure of 57% at 4 years when there are other devices without this impediment.

The freedom from rupture in this series would appear to be related to the small size of the aneurysms at graft implantation (mean, 50.5 mm) and the reduction in size of some aneurysms before undergoing expansion. If the same rate of expansion continues as occurred in the third and fourth years of follow-up in this study or the device is implanted in larger aneurysms, freedom from rupture cannot be expected to last. Endovascular AAA repair continues to evolve. If a problem is detected it needs to be addressed, not minimized.

INVITED COMMENTARY

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The study by Cho et al raises a number of interesting points, mostly reflecting questions that remain unanswered about endovascular repair in general. For example, there is nearly universal agreement that aneurysm enlargement following endovascular repair should be taken seriously. There is a lack of agreement, however, about what specific steps to take when an aneurysm enlarges with an endograft in place, especially if there is no obvious endoleak. It is logical that aneurysm growth reflects pressure within the sac and, thus, a failure to fully "depressurize" the sac. Many also assume that aneurysm growth with an endograft in place implies a risk of rupture equivalent to that of an unrepaired aneurysm, but this remains controversial.

This controversy is reflected in the Cho et al article, in which the authors appropriately report a higher-than-expected incidence of aneurysm enlargement with a specific endograft. As in many reports regarding endotension, however, the small patient num-